

Illicit Tramadol Tablets Traded in Kuwait during 2016 – 2017; Their Analysis by GC/MS and Classification

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/CJAST/2020/v39i1330683

Editor(s):

(1) Dr. Yahya Elshimali, Charles Drew University of Medicine and Science, USA

Reviewers:

(1) P. Brindha Devi, Vels Institute of Science, Technology & Advanced Studies (VISTAS), India.

(2) Abhik Chatterjee, Raiganj University, India.

Complete Peer review History: <http://www.sdiarticle4.com/review-history/57587>

Original Research Article

Received 20 March 2020

Accepted 26 May 2020

Published 04 June 2020

ABSTRACT

Aim: To determine the quality and quantity of tramadol traded in the State of Kuwait and its classification.

Study Design: Collected samples of tramadol tablets seized in Kuwait during 2016 & 2017 and a pure tramadol standard, all have been analyzed in the Forensic Laboratories.

Place and Duration of Study: All analyses were conducted during 2016–2017 in the Forensic Laboratories of the General Department of Criminal Evidences – Ministry of Interior – State of Kuwait.

Methodology: A total of fifty samples of non-pure tramadol tablets seized in Kuwait during the year 2016 & 2017 and one pure standard, all have been analyzed by using Gas Chromatography/Mass Spectrometry (GC/MS).

Results: The fifty collected samples of tramadol could be classified into three groups: The first (Red) group is recorded in 42 samples (84 % of samples) with concentration range between 0.1 mg/ml and 1.1 mg/ml; it has a red color known as (strawberry) which is a street name; it is mixed with carboxylic and silicic acids, the second (White) group is detected in 3 samples, with two different

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concentrations: One sample has 0.3 mg/ml and the other two samples have 0.4 mg/ml; it is mixed with acidic substances and newly identified venlafaxine and *the third (Medical) group* is recorded in 5 samples as a pharmaceutical drug with different colors and shapes, one of them was detected as acetaminophen, and hence deleted, while the concentrations recorded for all four tablets are 0.2 mg/ml; it is mixed with acidic substances and venlafaxine.

Conclusion: The main types of tramadol frequently traded in the State of Kuwait, can be divided into the following three groups: First Red Group includes red tablets which represent the most common type traded from Egypt, India and China according to the statistics of United Nations 2013(18), with purity range from 60% to 201%. The Second White Group includes all white tablets which are much less traded than the red tablets, with purity range from 58% to 123% and the Third Medical Group includes adulterated medical tablets which have purity range as 26%.

Keywords: Illicit tramadol tablets; GC/MS; classification; venlafaxine.

1. INTRODUCTION

Tramadol abuse has dramatically increased in the Middle East region, especially in Iran and Egypt. It has dramatically increased in Egypt since 2008 and has led to many admissions to addiction treatment centers. The widespread of tramadol use is due to its availability without prescription, its easy illegal smuggling and its cheap prices [1,2].

Tramadol(1R,2R)-2-(Dimethylaminomethyl)-1-(3-methoxyphenyl) cyclohexanol-1-ol [3,4] is an opioid analgesic used for the therapy of mild-to-moderate pain; tramadol overdose can cause acute liver failure; it can be addictive and weakly inhibits nor epinephrine and serotonin reuptake [5,6].

Tramadol is a synthetic drug, which explains its relatively weak affinity for opiate receptors. Frequent and regular administration is associated with tolerance and physical dependence, which may develop into addiction [7,6,8].

Tramadol is used worldwide and is listed in many medical guidelines for pain treatment. It is mentioned as analgesic for cancer pain relief. Tramadol is also listed on several national essential medicine lists. There is a growing evidence of the abuse of tramadol in some African and West Asian countries with large seizures of such preparations in North and West Africa. Abuse of tramadol is reported by Egypt, Gaza, Jordan, Lebanon, Libya, Mauritius, Saudi Arabia and Togo. Because of the increasing rate of abuse, Egypt has up-scheduled tramadol in 2009 [3,9,2].

The drug consumption has increased more than 10 times between 1993 and 2000 [9,8]. The pace

of growth in tramadol consumption was much higher than the fastest growing opioid analgesic drugs. Within the group of analgesic drugs, it would be difficult to explain such a rapid increase in tramadol consumption without considering its "regulatory advantage" on the competitive market for analgesic drugs [9,8].

In recent years, tramadol overdose has become one of the most common causes of poisoning admissions to emergency departments, while an increased rate of seizure due to tramadol poisoning has also been observed. It is reported that 15% to 35% of patients with tramadol overdose experience seizure [10,11,12].

In the State of Kuwait tramadol has been listed for a long time in psychotropic tables and then deleted, but afterwards tramadol trafficking to Kuwait has increased in recent years according to the statistics of Narcotics and Psychotropics Substance Section (NPSS) in General Department of Criminal Evidence from 38,782 thousand tablets in 2012 to 20,422.50 million tablets in 2017, and then to 31,015.50 million tablets in 2018 with ca. 124.8% increase during six years [13,14], and hence the drug was included again by a ministerial decision in 2011 at Schedule 4 [15,13,16].

In addition, the statistics of Forensic Medicine Department in Kuwait has recorded four death cases between tramadol addicts [15,13], which paves the way to carry out the present study with the main objective set to determine the chemical characteristics of tramadol traded in the State of Kuwait and give a new classification of it.

2. EXPERIMENTAL WORK

Selected samples of non-pure tramadol tablets seized in Kuwait and one pure standard tramadol

powder sample, all have been analyzed in the Narcotics and Psychotropic Substance Section (NPSS) (Forensic Laboratories, Ministry of Interior, Kuwait) by using Gas Chromatography/Mass Spectrometry (GC/MS) in accordance with analytical methods described by the Manual for Use by National Narcotics Laboratories and Clarke's Analysis of Drugs and Poison, for qualitative and quantitative analysis of tramadol in all tablets [4].

2.1 Sample Preparation

2.1.1 Pure standard samples

One external pure powder sample of tramadol has been supplied from Lipomed AG [17] to be used for quantitative analysis.

2.1.2 Non-pure samples

Fifty non-pure tramadol samples in tablet form have been collected from the seized cases investigated by the Forensic Laboratories during the years 2016 and 2017.

The pure and non-pure samples have been subjected to the same conditions: Each sample is 2mg in weight, dissolved in 2 ml of a solvent containing (Chloroform: Ethanol: Acetone) in ratio 70:20:10 and filtrated to injection with 1 µL in GC/MS.

2.1.3 Apparatus used for measurements

Gas Chromatography/Mass Spectrometry (GC/MS) has been used to analyze the tramadol samples and the standard at the same conditions of weight and solvent.

The following operating conditions have been applied in accordance with Agilent 7890B series Gas Chromatography "Operating Manual:

Operating conditions: The following operating conditions are in accordance with Agilent 7890B Series. Gas Chromatography Agilent technologies, with 5977B MSD (High Efficiency Sources), and 7693 auto sampler. "Operating Manual" [18]:

GC-MS Agilent Technologies 7890B GC system (integrated LAN) liquid samples and 5977B inert MS (mass selective) single quadrupole detector, with MSD in EI mode (electron ion source) and column (ULTRA 2) with 30 m x 250 µm x 0.25 µm with temperature limits from -60°C to 350°C with 7693 automatic sampler components

Injection Volume: 1.0 µl by syringe size 10.0 µl .

Inlet splitless with 280°C.

Ramp (temperature Column)

Initial: 100°C hold 4.00 min

Ramp: 8°C - 280°C hold 4 minutes (for 30.5 minutes)

Post: 300°C hold 5 minutes Run time (38.83 minutes)

Pressure: 8.97 psi.

Carrier gas (He) Helium with flow rate: 1.4

3. RESULTS

Being a well-known technique commonly used in the Forensic Laboratories in Kuwait GC/MS has been used for the analysis of seized tramadol samples to detect the main active substance (tramadol). Results obtained are as follows:

3.1 Determining Main Substances (tramadol) in Samples

A total of fifty samples have been collected as tablets with different color and shape to determine the main substance (tramadol), by using GC/MS. Fig. 1 shows that the red tablets are recorded in 42 samples, with % frequency in all samples 84% and with one sample giving negative result (caffeine), but all 41 samples are giving tramadol, mixed with excipients or additives; namely, carboxylic and silicic acids which are used as solvent (acidifying agent) to give the drugs design pharmaceutical form by regular pH, stability of active substance, and to improve their solubility or adsorption of active substances [19,20] and ethylgcridine as color substance. In case of the 3 samples with white color approximately 6% of samples have detected tramadol mixed with acidic substance and with *venlafaxine* as a new substance identified with the tramadol in the same tablet, which is described as antidepressant. Meanwhile, in the 5 samples identified as medical tablets 10% of the samples have different shapes and colors, with one of them detecting acetaminophen and hence deleted, while the other 4 samples have recorded tramadol, and acidic substances with *venlafaxine* [3,14].

3.2 Quantity Analysis of Main Substance (tramadol)

By calculating the concentration of tramadol in all three different colors (see Fig. 2), the tablets with red color have a weight varying between 290 mg and 350 mg and the concentrations of tramadol selected range from 0.1 mg to 1.1 mg with higher rate concentrate in 0.9 mg and 1mg, while the tablets with white color have a weight varying between 370 mg and 590 mg, with tramadol detected in two concentrations shown in Fig. 3: 0.3 mg in one table and 0.4 mg the other two tablets. Meanwhile, all four tablets identified as medical tablets with different mixed colors (see Fig. 3) have weight of 250 mg, with concentration of 0.2 mg each.

4. DISCUSSION

From the results of the analytical work made on tramadol tablets traded in Kuwait in the Forensic Laboratories, which have been received by NPSS (Narcotic Drugs and Psychotropic Substances Section) laboratory during the period 2016 to 2017, the following findings could be reached:

Tramadol tablets traded in the State of Kuwait could be classified into three types according to their color as summarized in Fig. 4; namely,

- *Type I Red tablets* known as "strawberry"; it is the main type traded in Kuwait with concentrations 0.1mg -1.1 mg; it is recorded in 41 samples(i.e.,84% of the samples), and is mixed with acidic and coloring substances,
- *Type II white tablets*: All tablets are white in color, and have concentrations between 0.3 mg and 0.4 mg, which are higher than those in the other type; they are mixed with the same acidic substances in addition to other antidepressant substance, known as venlafaxine, but have low distribution in Kuwait, and
- *Type III medical (mixed colored) tablets*: tramadol tablets traded in Kuwait such as medical tablets with different colors and shapes; have low concentration of 0.2 mg each; they are mixed like white tablets with acidic and venlafaxine substances, and have low distribution in Kuwait.

Fig. 5 demonstrates that the purification of tramadol as the main active substance in tablets traded in the State of Kuwait is in the range between 60% and 201% in red tablets, which are considered as the main type with the highest concentration compared with the white and medical tablets; followed by white tablets with a purification range between 58% and 123%, while the medical (mixed color) tablets have the same % concentration of 26% in all samples.

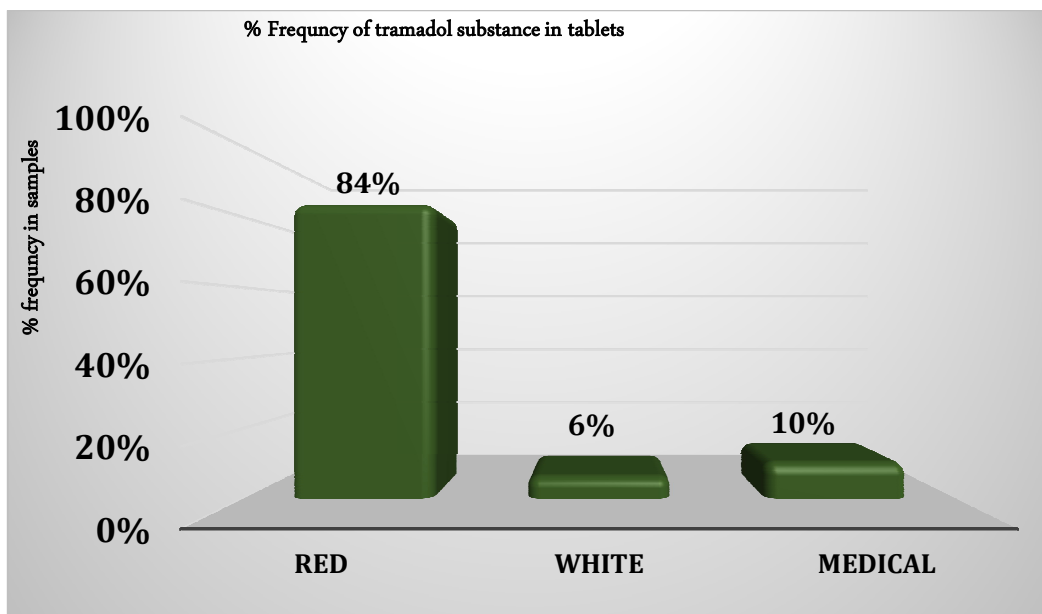


Fig. 1. %Frequency of tramadol in all samples of tablets

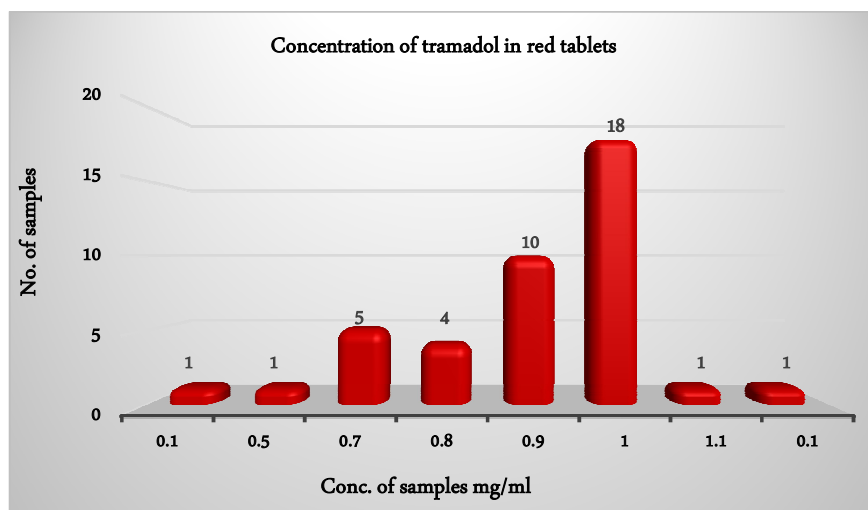


Fig. 2. Concentration of tramadol in red tablets

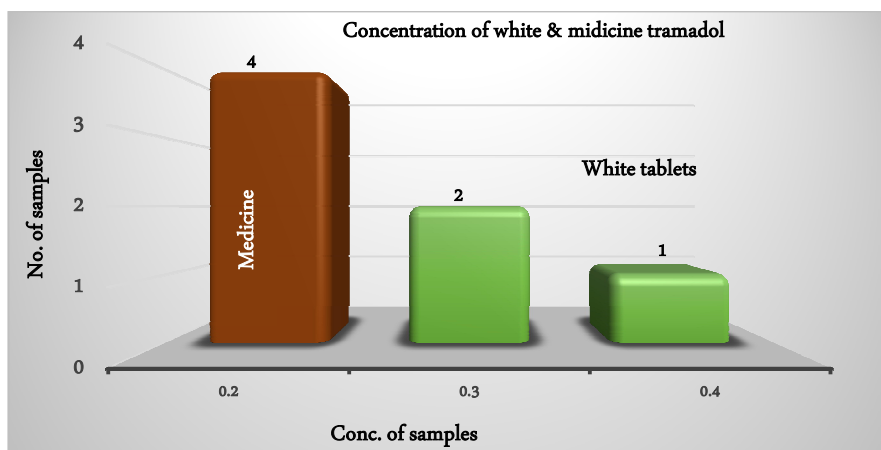


Fig. 3. Concentration of tramadol in white and medical tablets

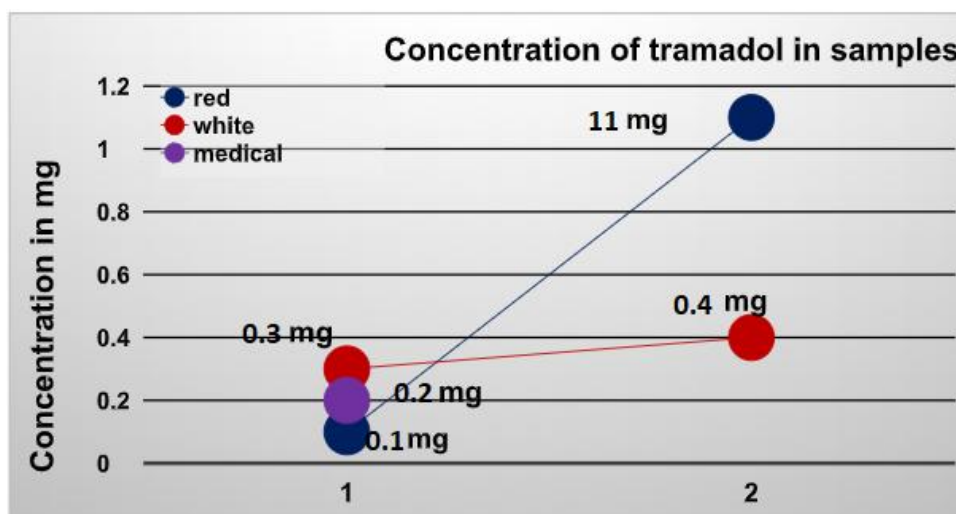


Fig. 4. Concentration of main active tramadol substances in all samples

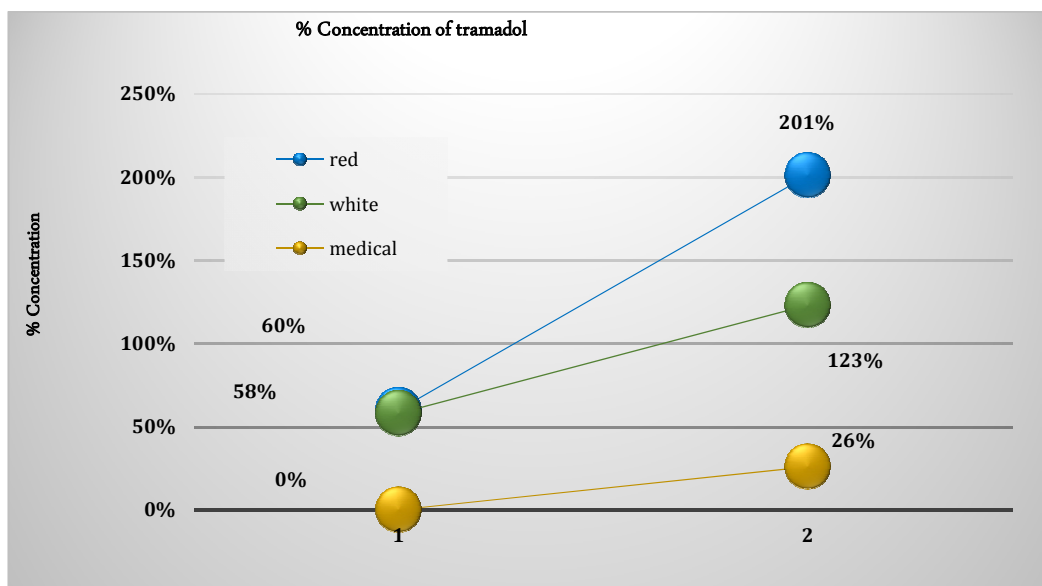


Fig. 5. % Concentration of main active tramadol substances in 2016 & 2017

5. CONCLUSION

Fifty samples of tramadol in tablet form have been collected during 2016 – 2017 and analyzed, with one sample of pure powder standard, in the Forensic Laboratories in the State of Kuwait, by using GC/MS. Tramadol traded in the State of Kuwait could be classified into three types; namely, Red Tablets, White Tablets and Medical Tablets. Red type is the main type traded in the State of Kuwait, while the other two types the white and medical (mixed color) tables have low distribution in the State of Kuwait. The difference between red and white tables are in the weight with concentrations of white tablets (370 mg – 590 mg) higher than those in red color tablets (290 mg – 350 mg). Tramadol Red tablets are mixed with acidic and coloring substances, while the white and medical tablets are mixed with acidic and venlafaxine substances.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
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